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07/827,187 01/28/92 BAKER R T-1092Y
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PATENT DEPARTMENT
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RAHWAY, NJ 07065-0907 ART UNIT PAF - N 114
12M2 1203 AS
DATE MAILED 05/18/93

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This application has been examined. Responsive to communication filed on 2/2/93. This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s). _____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892. 2. Notice re Patent Drawing, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449. 4. Notice of Informal Patent Application, Form PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474. 6. _____

Part II SUMMARY OF ACTION

1. Claims 1-18 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. Claims _____ have been cancelled.

3. Claims 9-12 are allowed.

4. Claims 1-6, 8, 13 are rejected.

5. Claims 7, 14-18 are objected to.

6. Claims _____ are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable, not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been approved by the examiner. disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed on _____, has been approved. disapproved (see explanation).

12. Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other

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15. Amendment filed in Paper No. 5, December 23, 1992 a declaration filed in Paper No. 6, January 19, 1993 and a supplemental amendment filed in Paper No. 7, February 3, 1993 have been entered and considered carefully.

Claims 1-18 are pending.

16. Confirmation and correction is hereby made with regard to the election of example 5, claim 6, p. 100 lines 25-26, N, N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-11+indol-2-yl]ethylamine. This oversight is regretted.

17. The improper Markush rejection of claims 1-8 is maintained for the following reasons:

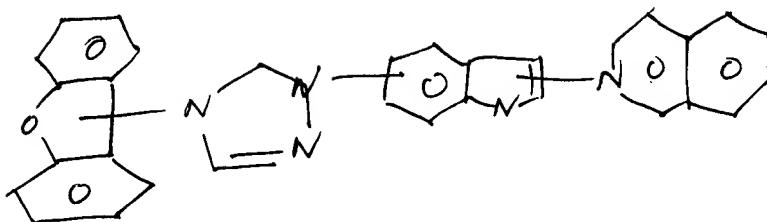
(1) In claim 6, the imidazolyl, tetrazolyl benzothiophenyl etc. compounds which are not in the now amended claim 1 have not been elected. A 112 fourth paragraph rejection will be made subsequently.

(2) The propriety of Markush grouping finds antecedent basis in MPEP 803.02 where it states:

"Broadly, unity of invention exists where compounds include within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility"

The alleged triazolylindolyl structure, being the common feature for the utility, is not a substantial structural feature for such claimed compounds e.g.

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for which, the other heterocyclic moieties constitutes major structural feature of the compounds.

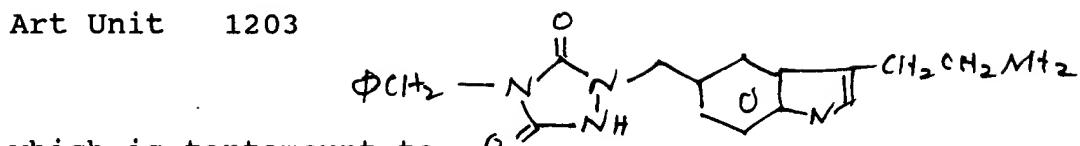
In addition, it is known in the indolyl amine, 5HT binding compound art, that small structural changes of the indolylamine compounds will result in drastic loss of biological activity (see Glennon cited on 1449, p. 6 last para.). In absence of factual evidence, there is insufficient support that all the diversified heterocyclic substituted compound i.e. "a heterocyclic group containing up to 18 carbon atoms and at least one heteroatom selected from oxygen, nitrogen and sulfur" would share the same utility as example 5.

18. The rejection of claim 1 under 35 USC 103 as being unpatentable over Robertson EP 313,397 is maintained for the following reason:

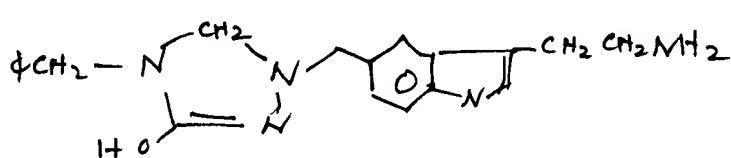
The examiner regrets the error of misdrawing the bondings of comp. 24 of Robertsons'. Applicants' drawing on p. 12 of the amendment (Paper No. 5) is correct. Robertson's example 24 is

(A)

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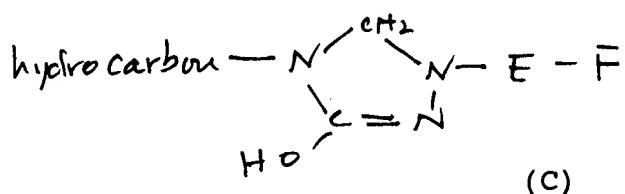


(A)



(B)

(based on generic teaching $Z=Z^1=C-$ or $-CH_2$) which is applicants' compound when X, Z, V are N, W, Y are C, $A_1=OH$ at W, $A^2=\text{hydrocarbon}$ at X that is



(C)

which is the tautomeric form of (B).

The arguments that applicants' compound are patentably distinct from Robertsons' triazolyl compounds in that applicants' triazolyl ring is always aromatic is incorrect. So far as claim 1 is concerned, both aromatic and non-aromatic rings are encompassed. Therefore, the rejection is maintained.

19. The rejection of claims 1-8 under 35 USC 103 over Robertson under 35 USC 103 is maintained.

Robertson taught both aromatic and non-aromatic ring system can be employed in similar type of compounds for treating migraines. Specifically, the dioxoimidazolinyl moiety is considered aromatic based on tautomerism. (See Katritzky Heterocyclic Chemistry p. 233). In addition, the comparative

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results submitted by applicants showing IC₅₀ for (1) and (2) (Paper No. 6, p. 2) are not persuasive. Compound (2) is not example 5. Example 5 has a dimethyl substitution of the amino groups.

The comparative data cannot overcome the rejection because:

- (1) Robertson taught heteroaromatic as well as heteroaliphatic ring system for W of Robertson's.
- (2) While the Declaration provided evidence that compound (2) is superior than Robertson's species, this superiority cannot be extrapolated to the generic claims which encompassed both heteroaromatic and heteroaliphatic rings.
- (3) The comparative result is limited to that aromatic triazoles is superior than aliphatic triazoles.

20. The following new grounds of rejection are directed to the newly amended claims.

Claims 4 and 6 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 4 embraced tetrazoles which are not in the base claim. Please note that the proviso statement requires one of Y² or Z¹ is "N", the other can be C or N, therefore, triazoles and tetrazoles.

Claim 6, imidazolyl and tetrazolyl compounds are not in the base claim 1.

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Claims 1-5, 8 and 13 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

base claim 1.

What does "cyclic hydrocarbon up to 18 carbon atoms" mean? Does this moiety including norbonyl or camphanyl? How are these compounds made? (1st para.)

If this term is ascribing only those as disclosed on p. 5 specification, the term lacks the particularity and specificity as required by the 2nd paragraph.

What does the term "a heterocyclic group containing up to 18 carbon atoms and at least one hetero atom selected from oxygen, nitrogen and sulfur" mean? Does this moiety include trithiazoles? How can such trithiazolyl compounds be made into pharmaceutical compositions? (1st para.) How do those diversified heterocyclic group containing compounds fit into the 5-HT_{1A} or 5HT_{1C} receptor sites which has "quite strict" structural requirements in its ligation. (See Glennon ref. 1449, p. 4 right col., last par.). (1st paragraph rejection).

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The term "aryl" is unclear. Does this term include 20 or more fused aromatic rings? for which enabling teaching is lacking (first par.). If this term is ascribing those as disclosed on p. 6, specification, the term lacks the particularity and specificity as required by the 2nd paragraph.

The term =N.G is ambiguous. The bonding to G should be consistent with the other bonding as a "--" not a period.

The term "migraine and associated clinical conditions" is unclear. What conditions are "associated clinical conditions"? It is recommended that the particular conditions be specifically pointed out as disclosed on p. 1 specification.

Claims 9-12 are allowable, because the Declaration showed superior IC₅₀ for unsubstituted aromatic triazolyl species.

Claims 7 and 14-18 are objected to because they are dependent on rejected base claims.

21. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM

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THE DATE OF THIS FINAL ACTION.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is (703) 308-4702.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

C. Warren Ivy
C. Warren Ivy
Supervisory Patent Examiner
Group 120

CHANG:jd
May 3, 1993
May 14, 1993